Insulin Autoimmune Syndrome (Hirata Disease): A Rare Case Report in an Indian Patient Dr. Ratnesh Singh Kanwar (MBBS, MD), Dr. Himanshu Jaiswal (MBBS, DRM Final Year Resident)

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Abstract

An unusual cause of spontaneous hypoglycemia is Insulin Autoimmune Syndrome (IAS) or Hirata Disease, characterized by high levels of insulinemia and circulating autoantibodies to insulin in subjects without prior insulin administration.To the best of our knowledge, this is the second case of IAS reported from India.

Insulin Autoimmune Syndrome (Hirata Disease): A Rare Case Report in an Indian Patient

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Abstract- An unusual cause of spontaneous hypoglycemia is Insulin Autoimmune Syndrome (IAS) or Hirata Disease, characterized by high levels of insulinemia and circulating autoantibodies to insulin in subjects without prior insulin administration. Till 2009, more than 200 cases from Japan and as many as 60 cases in Caucasians and 20 cases in East Asians have been reported. To the best of our knowledge, this is the second case of IAS reported from India.

Keywords - Hirata Disease, Insulin Autoimmune Syndrome, Autoimmunity, Hypoglycemia, Insulin Autoantibodies

Key Clinical Message - Hirata disease is an autoimmune syndrome rarely seen due to carbimazole/methimazole use in thyrotoxicosis. However, a clinician should keep it in mind when using these drugs and appropriate instructions to the patients should be issued.

Introduction- Insulin Autoimmune Syndrome (IAS) or Hirata Disease (HD), was first described by Hirata in 1970 and is characterized by spontaneous hypoglycemic episodes, a high titre of insulin autoantibodies and increased levels of immune reactive insulin in patients those who are not treated with insulin or oral hypoglycemic agents previously. There is a significant genetic predisposition to IAS as suggested by its association with specific HLA class II alleles, and it is often associated with previous exposure to drugs such as sulfhydryl group in their chemical structures such as Methimazole/ carbimazole. The majority of cases as reported in Japan, IAS is the third leading cause of hypoglycemia (325 patients diagnosed at the end of 2007).[1] The syndrome is rare in non-Japanese population: 60 cases in Caucasians and 20 cases in East Asians have been reported till date.[2, 3] To best of our knowledge, it is the second case reported in India.

Case Report- A 51 year old male of Indian origin, known case of hyperthyroidism on anti-thyroid drug (carbimazole) since 4 weeks, was brought to the emergency department of Maharaja Agrasen Hospital on 04-05-2019 with the complaints of: stretching and stiffening of hands, upward rotation of eyeballs and frothing from mouth. On investigation the plasma glucose level was found to be 52mg/dl. Intravenous 25% dextrose reversed the symptoms. There was no family history of diabetes. Neurology reference was done and subsequent Electroencephalogram revealed normal study. Patient had recurrent hypoglycemia for which endocrinology reference was done. The results of investigation dated 07-05-2019 were- **C-PEPTIDE SERUM** = 10.28ng/mL (0.81-3.85ng/mL),**INSULIN ANTIBODIES** = >300U/mL (<12.0 U/mL), **SERUM INSULIN RANDOM** = 241.9µU/mL (<140 µU/mL). Thyroid Function Test dated 24-05-2019 reveals TSH <0.01µIU/ml (0.3-5.5 µIU/ml), T3 = 362ng/dl (60-200 ng/dl), T4 = 18.4µg/dl (4.5-12 µg/dl). On CECT abdomen triple phase revealed pancreas in normal size, shape, outline and attenuation, no focal lesion seen. Patient was treated with 10 mCi of radioactive iodine (I – 131) in June 2019. Current thyroid profile report dated 22-08-2019 is TSH= 3.3µIU/ml (0.3-5.5 µIU/ml), T3 = 1.1ng/ml (0.4-1.81ng/mL), T4 = 7.9µg/dl (4.5-12 µg/dl). Thyroid profile dated 14.10.2019 shows patient going into post radioactive iodine ablation hypothyroidism with TSH= 113.67µIU/ml (0.3-5.5 µIU/ml), T3 = <0.10ng/ml (0.4-1.81ng/mL), T4 = <0.30µg/dl (4.5-12 µg/dl).

Discussion-Clinically, IAS present with symptoms of hypoglycemia, which can manifest either in the postprandial or in the post absorptive phases. This disease has no gender predilection. Its onset is quite often dramatic. Paradoxically, hyperglycemia can occur after a meal or glucose challenge.[4] In such patients, total serum insulin levels are very high as compared to those seen in the patients of insulinoma, in as much as insulin levels are just inappropriate and rarely more than 100 mU/L in the latter category.[3] However, serum-free insulin level may be normal or high with incomplete suppressed plasma C-peptide level. In such cases, serum proinsulin levels have also been noted to be very high. Insulin antibodies are typically polyclonal, although monoclonal antibodies have also been described.[5] IAS has been observed to be associated with the usage of drugs like insulin, sulfonylureas; SH-containing medicines (methimazole, captopril, penicillamine etc.), hydralazine, procainamide, isoniazid and α-interferone etc., in association with autoimmune disorders, plasma cell dyscrasias, alcoholic liver disease and organ transplant patients.[5] The disease is self-limiting in most of the cases. Most of the patients respond to small frequent meals - six or more times - in a day. Alfa-glucosidase inhibitors may sometimes be helpful in decreasing the postprandial levels of immunoreactive insulin resulting in reducing postprandial hypoglycemic episodes. Such patients who did not respond to the Alfa-glucosidase were treated with prednisolone, diazoxide, octreotide and plasmapheresis, with variable results. In the backdrop of the foregoing analytic review of the facts described above, it may be possible that the incidence of hypoglycemia has been part of the natural course of the disease, which is corroborated by the fact that there was spontaneous remission in 189 of 226 (83.6%) Japanese patients.[4]The exact mechanism of hypoglycemia in IAS is not known, but it is postulated that sulphydryl group interacts with disulfide bond in the insulin molecule, making the later more immunogenic. Most of the cases reported in Japan was because of the use of sulphhydryl group-containing drugs, while cases reported from other parts of the world are more frequently associated with autoimmune diseases or plasma cell dyscrasias.[3] Our patient was taking drug that contained sulfur and hydrogen atoms, namely carbimazole. Carbimazole is a prodrug that gets converted to the active form i.e., Methimazole. This activated form reacts by covalent binding with sulfhydryl group of cysteines. Thus it can be postulate that the activated form of sulfonamide may bind with disulfide bond in the insulin molecule, making the latter more immunogenic.

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Author Contributions-

1. Dr Ratnesh Singh kanwar – Consultation, diagnosis, and treatment of this patient. Writing of this manuscript.

2. Dr Himanshu Jaiswal – Radio-active iodine uptake, Radio-active iodine therapy of this patient. Writing and communication of this manuscript.**References** –1. Virally ML, Timsit J, Chanson PH, Warnet A, Guillausseau PJ. Insulin autoimmune syndrome: A rare cause of hypoglycemia not to be overlooked. Diabetes & Metabolism (Paris) 1999; 25:429-431. 2. Uchigata Y, Hirata SY, Iwamoto Y. Insulin autoimmune syndrome (Hirata Disease): Epidemiology in Asia including Japan. Diabetol Int 2010; 1:21-25. 3. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycaemia. Medicine (Baltimore) 2009; 88:141-153 4. Redmon JB, Nuttal FQ. Autoimmune hypoglycemia. Endocrinol Metab Clin North Am 1999; 28:603-18 5. Uchigata Y, Tokunaga k, Nepom G, Bannai M, Kuwata S, Dozio N, et al. Didderential immunogen determinants of polyclonal insulin autoimmune syndrome (Hirata's disease) and monoclonal insulin autoimmune syndrome. Diabetes 1995; 44:227-32**Conflict of interest statement** - We declare that there is no conflict of interest in the publication of this manuscript. This patient was managed at our institute and has given voluntary consent for the publication of this case report.